Food challenges: Patient selection, predictors, component testing, and decision points

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ABSTRACT

Background: *Oral food challenges are commonly used when there is uncertainty based on a clinical history as to whether a food allergy exists and to assess whether a food allergy has been outgrown.*

Methods: *A narrative review was performed, synthesizing available evidence in the literature.*

Results: *Because food challenges are generally multi-hour procedures that carry the risk for potentially severe allergic reactions, careful patient selection is important. Allergy tests can provide additional supportive information to guide decision-making but do not have sufficient diagnostic accuracy to replace food challenges in most circumstances.*

Conclusion: *Clinical history provides important clues with regard to the likelihood that a reaction may occur and should be combined with patient and family preferences and allergy test results when making decisions about pursuing food challenges.*

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Oral food challenges (OFC) play an important role in the accurate diagnosis of food allergy.[1,2] Because these procedures require time and effort, and carry risks for severe allergic reactions,[3] careful selection of patients and appropriate planning is necessary. A detailed clinical history is an essential element for assessing whether OFC may be indicated, and allergy testing can provide additional evidence to support decision-making with regard to OFCs.

PATIENT SELECTION

OFCs are generally pursued to establish the presence of food allergy, either for initial diagnosis or to determine whether an allergy has been outgrown. The clinical history can provide insight into the likelihood of allergy (pretest probability); details include timing of allergen exposure and symptom onset, quality and severity symptoms, response to treatment, presence of cofactors, and when the most recent exposure was.[3] If a clinical history demonstrates symptoms that are not consistent with immunoglobulin E (IgE) mediated allergy, then further evaluation is often not necessary. When a clinical history is convincing of allergy (*e.g.*, recent anaphylaxis within minutes of ingesting an allergen; high pretest probability), then OFCs would not be needed to confirm the allergy. OFCs provide important diagnostic information for patients who have no clinical history of reactivity and for those whose clinical history is not clear-cut. In addition, OFCs can be informative for families making decisions about whether to start treatments, *e.g.*, oral immunotherapy.

Additional considerations for pursuing OFCs include patient and family preferences (Table 1). The specific food allergen in question can influence decision-making, such as the nutritional impact of the food and presence (or absence) of the food in the family diet.[3] Some families may also consider whether their child would cooperate with OFC procedures, anxiety or apprehensions about the procedure and its outcomes, and implications on risk-taking behavior (*e.g.*, intentional ingestion at home if OFC is not performed). Other factors that must be considered, particularly in deciding when to schedule the OFC, include the status of other atopic and medical conditions because uncontrolled disorders may increase the risk for a severe reaction if the OFC is positive (*e.g.*, asthma) or complicate assessments during the OFC (*e.g.*, active rhinitis, acute urticaria).

SKIN TESTING AND SERUM ALLERGEN-SPECIFIC IgE

Skin prick testing (SPT) and serum specific IgE (sIgE) testing are routine allergy tests available to provide supporting information to the clinical history in making decisions with regard to OFCs for IgE-mediated food

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Table 1 **Considerations for pursuing OFC**

Medical Factors	Patient and Family Factors
Reaction history (*e.g.*, what food, how much, severity of symptoms)	Quality of life associated with the inclusion/exclusion of the food
Time since the most recent the reaction	Interest in adding food to the diet
Presence of cofactors	Ability to cooperate with OFC procedures
Nutritional impact of the food to be challenged	Anxiety or apprehensions about the procedure/ outcomes
Status of other atopic and medical conditions	Risk-taking behavior (e.g., intentional ingestion at home if OFC not offered)
	Interest in starting treatment for food allergy (*e.g.*, OIT)

OFC = Oral food challenge; OIT = oral immunotherapy.

allergies. SPT and sIgE tests have high sensitivity (ability to yield a positive result for patients with a food allergy), but low specificity (ability to yield a negative result for patients without a food allergy), so results must be interpreted in the context of the clinical history. Positive tests alone indicate the presence of allergen sIgE or sensitization and do not always indicate clinical reactivity.[1] Furthermore, test results do not reliably correlate with the severity of reactions nor do they predict thresholds (*i.e.*, eliciting dose at OFC).

Although diagnostic cutoffs have been published for SPT and sIgE values, cutoffs are variable across different studies, due to differences in study populations (*e.g.*, prevalence of allergy, age of included participants, presence of allergic comorbidities), food allergen, and study design (*e.g.*, inclusion and exclusion criteria, parameters for offering OFCs).[4–7] For some of the major food allergens (*e.g.*, milk, egg, peanut), 95% positive predictive values (PPV) (number of true positives of all positive values) for clinical reactivity have been published for SPT and sIgE (Table 2), based on studies of children seen at tertiary-care referral centers. Within these populations, results at these cutoffs indicate a high likelihood of clinical reactivity if the allergen is ingested, so many patients with these test results would not choose to undergo OFC. However, PPV is influenced by disease prevalence within a population, so interpreting test results against published PPVs must be done with caution if the patient population of a practice is different from the studied population. Moreover, OFCs may still be an important diagnostic tool despite high SPT or sIgE test results, especially if there are compelling reasons based on the clinical history or other patient factors. Even at test results reported to have a high PPV, clinical tolerance has been demonstrated for some patients by OFCs, which further supports the importance of clinical history and OFCs in the diagnosis of food allergy.[8,9] At levels < 95% PPV, OFC is often needed to determine whether allergy exists. OFCs can be performed safely and should be highly considered to establish a definitive diagnosis given the impacts of carrying a good allergy diagnosis and to provide relevant information for families who are deciding whether to commit to time and resource-intensive treatment, such as OIT. Of note, 95% PPV levels have not been published for every allergen, such as soy and wheat,[4] so OFCs play an key role in assessing clinical reactivity for many food allergies.

COMPONENT-RESOLVED DIAGNOSIS

Different proteins that comprise many of the major foods involved in IgE-mediated allergy have been characterized, and component-resolved diagnosis (CRD) entails measuring sIgE against specific proteins. CRD is commercially available for several allergens, but published cutoff levels and PPVs vary widely across studies, due to issues similar to studies of sIgE to whole-food extracts (*e.g.*, differences in prevalence of allergy across study populations).[10,11]

The role of component testing in a food allergy diagnosis is most extensively studied for peanut and

Table 2 **Published PPVs from specific studies for clinical reactivity to the major food allergens**

	sIgE 95% PPV	SPT 95% PPV[31]
Milk	Milk IgE: 15 kU_A/L (5 kU_A/L if <2 years)[4,32]	8 mm (6 mm if <2 years)
Baked milk	Casein IgE: 20.2 kU_A/L (69% PPV)[33]	—
Egg	Egg IgE: 7 kU_A/L (2 kU_A/L if <2 years)[4,34]	7 mm (5 mm if <2 years)
Baked egg	Ovomucoid IgE: 50 kU_A/L (>90% PPV)[15]	—
Peanut	Peanut IgE: 14 kU_A/L[4]	8 mm (4 mm if < 2 years)
Soy	Soy IgE: 65 kU_A/L (86% PPV)[4]	—
Wheat	Wheat IgE: 100 kU_A/L (100% PPV)[4]	—

PPV = Positive predictive value; sIgE = specific immunoglobulin E; SPT = skin-prick test.

hazelnut. These nuts have proteins homologous to a birch pollen allergen (Bet v 1) that can result in a positive sIgE testing result to peanut and hazelnut in patients who have birch tree pollen allergy, yet they may not have reactions if these foods are eaten. The birch pollen homologous proteins are Ara h 8 (peanut) and Cor a 1 (hazelnut), and component testing to these proteins, along with other peanut and hazelnut proteins can provide important insights to guide management. For example, if there is isolated sensitization to these Bet v 1-homologues in a individual with pollen allergy, then the patient is likely not at high risk for anaphylaxis after ingestion of these nuts. However, if testing demonstrates a high quantity of sIgE directed at the major allergens in peanut or hazelnut, counseling on allergen avoidance and management of acute allergic reactions in the event of accidental ingestion would be important.

Among the peanut component proteins, sIgE to Ara h 2 has been identified as the best predictor for allergy. The 2020 practice parameter[12] on peanut allergy diagnosis used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology and determined that sIgE to Ara h 2 has the best diagnostic accuracy based on optimal positive and negative likelihood ratios (positive likelihood ratio = sensitivity/(1 – specificity), how much a positive test increases the probability of allergy; negative likelihood ratio = (1 – sensitivity)/specificity, how much a negative test decreases the probability of allergy) (certainty of evidence for the recommendation: low certainty evidence). Although this test has high specificity, compared with SPT and sIgE to whole peanut extract, Ara h 2 IgE testing has lower sensitivity. There was insufficient evidence to support the use of Ara h 2 IgE to predict future reaction severity when used as a continuous variable, and analysis of specific cutoff levels of 2 and 50 kU_A/L for sIgE to Ara h 2 had low sensitivity and specificity (*i.e.*, Ara h 2 sIgE at 2 kU/L has sensitivity of 0.78 and specificity of 0.45).

With regard to tree nuts, Cor a 9 and 14 are the major hazelnut allergens associated with clinical reactivity. Studies have assessed the diagnostic utility of CRD for hazelnut components, and systematic reviews and meta-analyses note that both Cor a 9 and 14 are good discriminators of hazelnut OFC outcomes, with Cor a 14 slightly out-performing Cor a 9.[13,14] Cutoff levels were examined in a meta-analysis of eight studies; Cor a 14 sIgE of 0.35 kU_A/L and Cor a 9 sIgE of 1.0 kU_A/L had the highest diagnostic accuracy.[13] Another systematic review found that there was no clear consensus across studies for the optimal cutoff for component testing in diagnosing hazelnut allergy.[14] Component testing for other tree nuts is less studied; IgE to Ana o 3 and IgE to Jug r 1 have been identified as having a high diagnostic value for cashew and walnut allergy, respectively, but cutoff levels have not been established.[14]

Component testing has been explored for milk and egg allergy (Table 2), particularly for determining status of baked milk or baked egg tolerance because this can have important implications for expanding a patient's diet and improving quality of life. The presence of IgE to casein (Bos d 8), the major milk allergen, is associated with a more persistent allergy phenotype, including higher severity of reactions. However, the diagnostic utility of casein IgE in determining baked milk tolerance is unclear. Similarly, conflicting data exist with regard to the utility of IgE testing to ovomucoid (Gal d 1), the dominant egg allergen, in predicting baked egg tolerance. Some studies report that IgE testing to ovomucoid outperformed egg white SPT and whole egg sIgE,[15] but these findings were not replicated in other studies.[16] Differences in study designs likely contribute to these conflicting results for milk and egg component testing.

NEWER TESTS

Epitope Analysis

IgE antibodies are targeted to specific parts of allergen proteins, and epitope assays allow for more detailed profiling of IgE binding. Peptide microarray was an early form of epitope analysis, and these studies found correlations between IgE binding affinity and epitope diversity with severity and persistence of milk allergy[17,18] and with symptom severity and eliciting dose in OFCs to peanut.[19] The new bead-based epitope assay (BBEA) assesses IgE and IgG4 binding to > 90 sequential epitopes. BBEA for peanut has high sensitivity (92%), specificity (94%), PPV (91%), and negative predictive value (95%), with higher diagnostic accuracy compared with peanut SPT, sIgE, and component testing in validation studies when using the Consortium of Food Allergy Research (CoFAR2) and Peanut Oral Immunotherapy Study: Safety, Efficacy and Discovery (POISED) cohorts.[20] In addition, BBEA has high accuracy in predicting thresholds at peanut food challenge (cumulative tolerated dose).[21] Work is on-going to evaluate BBEA for the diagnosis of food allergies as well for exploring BBEA as a biomarker for monitoring immunotherapy response.[22–24]

Basophil and Mast Activation Tests

The basophil activation test (BAT) and mast cell activation test (MAT) are cellular tests that hold promise for food allergy diagnostics. The BAT is a functional *in vitro* test that measures basophil surface activation markers after stimulation by an allergen (either whole allergen extracts or individual allergen components). Although BAT has high specificity, sensitivity, PPV, and negative predictive valve,[25,26] and may predict

reaction severity and threshold in the studied populations,[27,28] the requirement for sample processing within 24 hours of the blood draw makes it difficult to incorporate into routine use. In addition, there is a 10–15% nonresponder rate (basophils do not respond to stimulation despite expressing normal density of IgE on the cell surface and upregulate CD63 in response to an IgE-independent stimulus), which is an important limitation for clinical use.[29]

MAT can use stored serum and plasma samples to sensitize mast cells and has high specificity and PPV for peanut allergy similar to BAT.[30] However, MAT has lower sensitivity and negative predictive value; further studies are needed to determine the clinical utility of MAT for food allergy.

CONCLUSION

OFC is an essential tool in food allergy diagnosis, but pursuing this time- and resource-intensive procedure requires careful patient selection. The medical history as well as patient and family factors are important factors to consider when making the decision to undergo an OFC. SPT and sIgE (whole allergen and components) provide additional information, but results do not always correlate with clinical reactivity, and these tests do not provide insights into thresholds or reaction severity. Newer tests seem to have improved diagnostic accuracy and may help reduce the need for OFCs; further standardization and validation would support adoption of these tests into routine clinical practice and establish their role in the diagnostic workup for food allergy.

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